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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/685,061	10/06/2000	James M. Robl	P 0275492 23523-0168	7154

7590 01/30/2002

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EXAMINER
TON, THAIAN N

ART UNIT	PAPER NUMBER
1632	9

DATE MAILED: 01/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/685,061	Applicant(s) ROBL ET AL.	
	Examiner Thaian N. Ton	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *26-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25 and 31-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice To Comply* .

DETAILED ACTION

Applicant's election without traverse of Group I, claims 1-25, and 31-50 in Paper No. 8 is acknowledged. Claims 1-50 are pending, however, claims 26-30 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8.

Claims 1-25 and 31-50 are under current examination.

Sequence Compliance

This application fails to comply with requirement of 37 CFR 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Each nucleotide and/or amino acid in the instant application must be accompanied by "SEQ ID NO:". See p. 46, lines 12-15 of the application. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821-1.825).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-25 and 31-50 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4-19, 21-30 and 32-57 of copending Application No. 09/260,468. Although the conflicting claims are not identical, they are not patentably distinct from each other, because the instant application is directed to a method of cross-species nuclear transfer using differentiated human or mammalian cell or cell nucleus and an enucleated animal oocyte, and the '468 Application is directed to using an adult differentiated human cell or cell nucleus in an enucleated bovine oocyte. As such, the species of human differentiated cell and bovine oocyte makes obvious the genus of mammalian differentiated cell and animal oocyte.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 18-23 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are directed to "embryonic or stem-like cells" and "human embryonic or stem-like cells". As written, the claims read on cells that are a human embryo. A human being or human embryo is non-statutory subject matter. See 1077 O.G. 24, April 21, 1987.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 and 32-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method for the production of human or mammalian embryonic or stem-like cells comprising inserting a differentiated human or mammalian cell or nucleus into an enucleated bovine oocyte under conditions suitable for the formation of a nuclear transfer (NT) unit; activating the NT units; culturing the activated NT units until greater than the 2-cell developmental stage; and culturing cells obtained from said cultured NT units to obtain human or mammalian embryonic or stem-like cells.

The specification discloses the preparation of nuclear transfer units via a method of nuclear transfer of adult human epithelial cell nuclei into enucleated cattle oocytes to form a nuclear transfer (NT) unit (Figure 1) by electrofusion

techniques. The methods disclosed in Example 1 of the specification result in the production of 1 NT unit (16-400 cell stage) according to Table 1, page 42. The specification further teaches that interspecies NT can be used to clone a gaur using cross-species nuclear transfer into an enucleated bovine oocyte, with normal karyo- and phenotypic development through attachment and later stages of fetal growth, with the differentiation of complex tissues and organs (see Example 2, p. 43). In particular, the specification teaches that donor dermal fibroblasts were isolated from an adult male guar. Enucleated bovine oocytes were obtained for nuclear transfer. Following NT, the fused complexes were then analyzed and the resulting blastocysts were transferred into recipient females. Three fetuses were analyzed for confirmation of genomic origin and fetal fibroblast cell lines were derived. These cells were cytogenetically analyzed and mitochondrial DNA and microsatelliteDNA was also analyzed. The specification teaches that cytogenetic analysis of the cloned cell strains revealed a normal karyotype with a chromosome number of 58, identical to the donor fibroblast (see p. 47, line 29). Microsatellite analysis showed that the cloned cell strains had *gaurus* nuclear background (see p. 48, lines 1-2). Analysis of the mitochondrial DNA (mtDNA) found that no *gaurus* mtDNA was present, and that the mtDNA was contributed to the bovine oocytes.

Although the methods of the instant invention result in the production of 1 NT unit of which the specification reports propagates into what appears to be ES-like cell colonies (as determined by cell morphology) in Example 1, and the production of fetal mammals using interspecies NT (Example 2), the specification fails to demonstrate that the ES-like cells function in Example 1 as true ES-cells in that they are in fact totipotent or that they function as stem cells in that they are capable of differentiation into other multilineage cell-types. As such, the

specification fails to enable the production of embryonic or stem-like cells as recited in step (iv) of Claim 1.

The unpredictability of the method of NT transfer, as a whole, lies in the need to convert a differentiated cell to a totipotent cell (embryonic stem cell). Cells contain the same DNA complement, however, in differentiated tissues, not all DNA sequences are expressed. For example, a liver does not make rhodopsin and retinal cell structures, and retinal cells do not make clotting factors and hepatocyte structures. For a cell to go through all the steps of development, it, or its nucleus, must be reverted to the stage where all DNA sequences can potentially be expressed, and expression regulated according to developmental stage. The specification has not provided evidence that the cells produced by the described methods are true pluripotent cells (embryonic stem cells or embryonic or stem-like cells). The specification fails to demonstrate whether the ES-like cells stain positive for alkaline phosphatase (AP), exhibit the formation of embryoid bodies, spontaneously differentiate into at least two different cell types, or express exclusive ES cell markers. The specification only discloses several morphological characteristics (Example 1). Further, it is not predictable (without specific guidance) whether the claimed ES-like cells are even cells which are capable of differentiation upon induction to a particular cellular pathway, e.g., lineage or multilineage precursor. The specification teaches that the prior art is lacking in the production of inner cell mass cells from NT units useful to form ES cell-like colonies that could be propagated (page 6, lines 19-22). Thus, the skilled artisan would not have found guidance from the art on the methodology of nuclear transfer utilizing differentiated adult human or mammalian cells or nuclei for insertion into bovine enucleated oocytes. For this, the artisan could **only** rely on the instant specification

and in light of the very low frequency of NT units produced by the method, the lack of a showing demonstrating differentiation from the produced cells, and the lack of evidence demonstrating ES cell totipotency; the claimed invention is not enabled by the specification. As such, as the specification discusses "how to use" cells obtained from the NT process for production of differentiated cells useful for cellular transplantation, it is unknown how the skilled artisan would be able "to use" the claimed cells (embryonic or stem-like cells) in a manner which is consistent with the specification without specific guidance.

Applicants rely on prior art methods for induction of differentiation using their resulting embryonic or stem-like cells. However, differentiation of ES cells is species-dependent. This observation is supported by Stice et al. (Theriogenology, 1998) who disclose that "[o]verall, an obvious conclusion of mammalian nuclear transfer studies is that the results obtained often depend on species investigated in the study." (See page 130, Species Specific Difference, 1st paragraph). Further, Stice et al. discuss that the degree of differentiation depends on the source of terminally differentiated nuclei as well as other factors (paragraph bridging pages 131-132). Thus, it is inappropriate to rely on the prior art with respect to mouse (or any other species) ES cell differentiation techniques as it applies to the embryonic or stem-like cells of the instant invention. It is also not clear from the specification what contribution (functionally or structurally), if any, the bovine cytoplasm (or mitochondria) makes to the resulting embryonic or stem-like cell of the instant invention. Further, in view of structural (or functional) differences in the ES-like cells of the instant invention, the skilled artisan would not reasonably expect to induce differentiation into other cell lineages using techniques in the art available for mouse ES cells. As such, the specification fails to provide guidance and direction

for critical parameters of the claimed invention with respect to obtaining true totipotent embryonic stem cells which give rise to germline tissue and the whole animal, or even embryonic cells which are merely capable of differentiation, for example.

Further, with regard to the structure and function of the cells produced by the NT methods of the invention, Dominko et al. (Biology of Reproduction, 1999) support that cross-species NT cannot be judged as useful before nuclear reprogramming, somatic cell/recipient cytoplasm compatibilities are examined. See page 1501, last paragraph. With regard to examining nuclear reprogramming or dedifferentiation, Dominko et al. disclose that such can only be determined by demonstration of a pregnancy carried to term. As Dominko et al. only teach that bovine cytoplasm has the ability to support several mitotic cell cycles directed by newly introduced nuclear DNA, importantly, they note that "[w]hether this introduced differentiated DNA is reprogrammed, is modified, or simply remains unchanged is currently under investigation." See page 1501, column 1, first paragraph. As such, in view of the supported undeveloped and unpredictable state of the art with respect to the characterization of cells produced by cross-species NT, Applicants' demonstration of the production of only one NT unit (Table 1) cannot be extrapolated to the production of embryonic stem cells as known in the art or as precursor cells as known in the art.

The courts have stated that:

A specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure** of any specific

starting material or **of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.** Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

In the instant case, the specification fails to provide guidance to the skilled artisan on any parameters which would be necessary and critical for the production of human or mammalian embryonic or stem-like cells by the cross-species NT process which exhibit embryonic stem cell properties or even mere differentiation upon induction.

Furthermore, the specification in particular, has not provided a use for human embryonic stem (ES) cells made by the method in that such cells, if true ES cells, have the potential upon transfer to a host to develop into a human being. As certain of the product claims recite "human embryonic or stem-like cells", this argument is proper in that the term "embryonic stem cell" has a well known potential in the art to give rise to the corresponding species of animal. It is acknowledged that the specification contemplates the production of human stem cell multilineage precursors, however, since the specification also discusses the ES cell potential for germ-line manipulation (pages 2-8) with respect to ES cells of non-human mammalian species, it is not clear how and under what circumstances, humans would be so made from the ES-like cells of the invention.

It is noted that it appears that the state of the art, as it specifically pertains to the instant application and claimed invention, is clearly lacking in supported evidence. In particular, Marshall (Nature, 1998) discloses that "Robl concedes that the experiment did not yield publishable data" (see col. 3, 1st full paragraph) and that [Robl] "classified the cells as human stem cells based on his experience of 'looking at hundreds and hundreds' of cell colonies." Marshall discloses, that at that time, none of the normal tests had been performed to demonstrate that these cells were human or that they were stem cells. Furthermore, Marshall reports that one skilled in the art, had stated that the cells in question had met none of the criteria for embryonic stem cells. As such, it would have required undue experimentation for one skilled in the art to perform the claimed methods of NT transfer for production of cells which meet the criteria of a true embryonic stem cell, or rather a stem cell of sort, which upon differentiation, would provide cellular or gene therapy upon transplantation. A nexus must be provided between the production of their one NT unit and claims directed to "embryonic or stem-like cells" and claims directed to using differentiated cells for cellular transplantation and gene therapy.

With regard to claims 32-42, the specification fails to teach the gene modification of any differentiated cell produced by their methods, and in fact, fails to perform differentiation assays using the produced NT unit. The specification additionally fails to teach the use of gene-modified differentiated cells as a starting point in the method of cross-species nuclear transfer. As such, the specification fails

to enable the gene-modification of cells for use in the methods or as produced by the methods.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction and/or guidance provided by the specification, the absence of working examples for the demonstration of or reasonable correlation to producing human or mammalian embryonic or stem-like cells capable of mere differentiation, for example, the unpredictable and undeveloped state of the art with respect to cross-species nuclear transfer (using adult differentiated nuclei) for production of embryonic stem cells which give rise to germline tissue and the whole animal or which may be induced to differentiate, in particular with respect to carrying out a process involving insertion of differentiated, adult human cell nuclei into bovine oocytes, the unpredictable state of the art with respect to extrapolating results obtained from ES cells of different species of animals to results obtained from chimeric bovine/human embryonic or stem-like cells, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-25 and 31-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1, 15, 16, 18-23, 32, and 34, the phrase "embryonic or stem-like cells" is vague and indefinite with respect to structure and function of the cells. For example, do Applicants intend to claim embryonic stem cells, stem cell progenitors or precursor cells, or both? Applicants refer to the term "stem cell-like" with respect to the contribution of the bovine oocyte mitochondria, however, does such a structural contribution have any effect on the function of an embryonic stem cell, such that the resulting cells can not be termed embryonic stem cells? If the contribution of bovine mitochondria has absolutely no effect on the function of the resulting embryonic or stem-like cell of the invention, then how is the cell distinguished over human or mammalian ES cells known in the art? Or human stem cells known in the art? Clarification and/or amendment to the claims is requested. Note that claims 2-35 depend from claim 1.

In claims 1, 32, 33, and 35, the term "desired" is vague and indefinite as to what is intended to be encompassed with respect to the metes and bounds of a "desirable" gene or cell. Clarification and/or amendment to the claims is requested. Claims 2-35 depend from claim 1.

Claim 31 recites the limitation "which contain and express an inserted gene" in line 2. There is insufficient antecedent basis for this limitation in the claim. The

claim depends from a claim directed to cells obtained by a method which does not involve gene modification. Amendment to the claim is required.

Claim 32 recites the limitation "wherein a desired gene is inserted, removed or modified" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim. The claim depends from a method which does not involve gene modification. Amendment to the claim is required. Claims 33-35 depend from claim 32.

Claim 46 is vague and indefinite in the recitation "a DNA that encodes to a detectable marker, the expression of which is linked to a particular cyclin." It is unclear if the claim is drawn to a fusion protein or the "particular cyclin" is a promoter sequence which controls expression of the detectable marker. Clarification and/or amendment to the claim is requested. Claims 47-49 depends from claim 46.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 18 is rejected under 35 U.S.C. 102(b) as being anticipated by Bradley et al. (Biotechnology, 1992).

Claim 18 is directed to embryonic or stem-like cells. Note that it is only the product which is anticipated by the prior art and not the process by which the product is made. This is because the final product (the embryonic or stem-like cells) is not distinguished by any particular features or characteristics as a result of the process by which it is made. As such, the limitations of the claimed cells are met by any embryonic or stem-like cell in the prior art. As such, note that it is not clear as to what the phrase "embryonic or stem-like cells" encompasses. See rejection under 35 U.S.C. §112, second paragraph. Thus, in the instant rejection, the phrase is being interpreted as embryonic stem cells.

Bradley et al. teach mouse embryonic stem cell lines AB1, AB2.1, and CCE, which display germline transmission.

Accordingly, Bradley et al. clearly anticipate claim 18.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 18-25 are rejected under 35 U.S.C. 102(e) as being anticipated by Tsukamoto et al. (US Patent 5,716,827).

The claims are directed to human embryonic or stem-like cells. Note that it is only the product which is anticipated by the prior art and not the process by which the product is made. This is because the final product (the embryonic or

stem-like cells) is not distinguished by any particular features or characteristics as a result of the process by which it is made. As such, the limitations of the claimed cells are met by any embryonic or stem-like cell in the prior art. As such, note that it is not clear as to what the phrase "human embryonic or stem-like cells" encompasses. See rejection under 35 U.S.C. §112, second paragraph. Thus, in the instant rejection, the phrase is being interpreted as human stem cells.

Tsukamoto et al. disclose the production of human hematopoietic stem cells capable of producing members of each of the hematopoietic lineages, *i.e.*, differentiated cells (See Abstract and claims 1 & 2). Thus, without a distinction indicating a structural or functional difference of the claimed cells, the human hematopoietic stem cells and differentiated cells produced therefrom taught by Tsukamoto et al. clearly meet all of the limitations of the claimed cells.

Accordingly, Tsukamoto et al. clearly anticipate the claimed invention.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 18-23 are rejected under 35 U.S.C. 102(a) as being anticipated by Granerus et al. (Cell Proliferation, 1996, pp. 309-314).

The claims are directed to human embryonic or stem-like cells. Note that it is only the product which is anticipated by the prior art and not the process by which the product is made. This is because the final product (the embryonic or stem-like cells) is not distinguished by any particular features or characteristics as a result of the process by which it is made. As such, the limitations of the claimed

cells are met by any embryonic or stem-like cell in the prior art. As such, note that it is not clear as to what the phrase "human embryonic or stem-like cells" encompasses. See rejection under 35 U.S.C. §112, second paragraph. Thus, in the instant rejection, the phrase is being interpreted as cells which exhibit similar properties as that of human embryonic stem cells.

Granerus et al. disclose a human cell line, Tera 2, which functions in several aspects as a human embryonic stem cell (See Abstract). Thus, without a distinction indicating a structural or functional difference of the claimed cells, the human cells of Granerus et al. having embryonic stem cell activity meet all of the limitations of the claimed cells.

Accordingly, Granerus et al. clearly anticipate the claimed invention.

Claims 18-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamane (Japanese Journal of Cancer and Chemotherapy, 1987).

Note that the same product-by-process analysis is applied here as in the preceding rejections. The claims are not clearly defined (112/2nd) or enabled (112/1), thus, the phrase "human embryonic or stem-like cells" is not distinguishable over human differentiated cells.

Yamane disclose human differentiated cells derived from epithelial cells, skin keratinocytes and endothelial cells (See Abstract). Thus, without any distinction indicating a structural or functional difference of the claimed cells, the human differentiated cells of Yamane meet all of the limitations of the claimed cells.

Accordingly, Yamane clearly anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tsukamoto et al. (US Patent 5,716,827).

Claim 31 is directed to human differentiated cells which contain and express an inserted gene.

Tsukamoto et al. disclose recombination techniques known in the prior art for insertion of a gene of interest into mammalian cells. See column 8, lines 9-11.

Accordingly, it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify differentiated human cells produced by stem cell precursors to comprise a gene of interest with a reasonable expectation of success.

Thus, the claimed invention, as a whole, was clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolfe et al. (Theriogenology, 1990) taken with Collas et al. (Molecular Reproduction and Development, 1994).

The claims are directed to a method of producing human embryonic or stem-like cells via nuclear transfer of a differentiated human or mammalian cell nucleus

to an animal oocyte. See 112, 2nd rejection with regard to the indefiniteness of the limitation "embryonic or stem-like cells". It is unclear what cells result from the culture of NT units in the absence of a showing of unexpected results by Applicants relating to the production of true ES cells or differentiation capacity of the ES-like cells of the invention. As such, the cited prior art is interpreted to provide sufficient motivation to select cross-species differentiated mammalian cell nuclei and oocytes for use in nuclear transfer methodology with a reasonable expectation of producing at least one nuclear transfer unit of which is capable of being cultured into any type of cell which meets the limitations of "embryonic or stem-like" cell.

Wolfe et al. teach a method of cross-species nuclear transfer using nuclei from bovine preimplantation embryos and oocytes of a varying species. Wolfe et al. disclose the production of blastocysts derived from bovine nuclei and bison ovum as well as bovine nuclei and goat ovum. Thus, the experimentation of Wolfe et al. demonstrates that mammalian nuclei may be capable of interacting with cytoplasm from other mammalian species to support normal development (See Abstract). Wolfe et al. differ from the claimed invention in that they do not propose nuclear transfer of human or mammalian differentiated nuclei into bovine oocytes. However, at the time the claimed invention was made, Collas et al. disclose results indicating that transplanted differentiated nuclei may be pluripotent. Collas et al. also suggest that "a variety of differentiated mammalian cell types may promote early preimplantation development of NT embryos." (See page 266, Discussion).

Accordingly, in view of the collective cited prior art, it would have been obvious for one of ordinary skill in the art to select human or mammalian differentiated cell nuclei and animal oocytes of a varying species for use in nuclear transfer with a reasonable expectation of producing at least one nuclear transfer

unit of which is capable of being cultured into cells which meet the limitation of "embryonic or stem-like" cells.

Note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988).

Thus, the claimed invention, as a whole, is clearly prima facie obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Claims 32-50 appear to be free of the cited prior art of record because the cited prior art of record fails to teach or suggest cross-species nuclear transplantation to obtain using donor cells which are gene modified or to produce cells which can be gene-modified and useful for cell transplantation. However, these claims are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Clark, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Patsy Zimmerman, Patent Analyst, at (703) 305-2758. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
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